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ORIGINAL ARTICLE

Risk factors of incomplete response to proton pump inhibitor therapy in patients with mild erosive esophagitis

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Summary *Background:* Incomplete symptom resolution to proton pump inhibitor (PPI) therapy is a common problem in the treatment of gastroesophageal reflux disease (GERD). The aims of this study were (1) to examine the rate of incomplete symptom response following 8-week PPI therapy in patients with mild erosive esophagitis (Los Angeles Grade A/B erosive esophagitis) and (2) to determine the independent factors predicting incomplete symptom response in patients with mild erosive esophagitis.
Methods: From January 2010 to July 2012, symptomatic GERD patients with endoscopic findings of Los Angeles Grade A or B erosive esophagitis were recruited for the study and received esomeprazole 40 mg daily for 8 weeks. The characteristics of eligible patients including clinical factors, endoscopic findings, *Helicobacter pylori* status, and *CYP2C19* (cytochrome P450 2C19) genotype

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were checked on enrollment. Patients were asked to record symptoms with diary cards during the follow-up period. The major outcome measurement was incomplete symptom response.
Results: In total, 232 patients (male/female, 126/106) participated in this study. Following 8-week esomeprazole therapy, 50 (21.6%) of the patients had incomplete symptom response. Univariate analysis showed that sex, alcohol consumption, underlying diseases, regurgitation of food, chest pain, globus, and insomnia were associated with incomplete symptom response ($p = 0.049$, $p = 0.006$, $p = 0.023$, $p = 0.010$, $p = 0.013$, $p = 0.009$, and $p < 0.001$, respectively). Multivariate analysis with stepwise logistic regression revealed that only globus [95% confidence interval (CI): 1.185—4.897; $p = 0.015$] and insomnia (95% CI: 1.289—3.018; $p = 0.002$) were independent risk factors for incomplete symptom response with odds ratio (OR) = 2.4 and OR = 2.0, respectively.
Conclusion: Of the patients with Los Angeles Grade A/B erosive esophagitis, 21.6% failed to have complete symptom resolution following 8-week PPI therapy. Globus and insomnia are two independent factors predicting incomplete symptom response in patients with mild erosive esophagitis.

Introduction

Gastroesophageal reflux disease (GERD) is a common acid-peptic disorder characterized by recurrent troublesome reflux symptoms and esophageal injury. It is the strongest known risk factor for esophageal adenocarcinoma [1,2]. Many studies indicated that the prevalence of GERD is markedly higher in Western populations than in Asian populations [3—6]. However, the prevalence of GERD has increased in Asia in recent decades [7,8]. Our studies demonstrated that the recent prevalence of GERD in the general population and erosive esophagitis in patients undergoing health check-ups in Taiwan were 25% and 17%, respectively [7,8]. The reasons for the increasing prevalence of erosive esophagitis in Asia remain unclear, but are probably related to the changes in lifestyles, westernization of diet, lack of exercise, aging of population, and a decrease in *Helicobacter pylori* infection [9].

Currently, therapy for erosive esophagitis largely focuses on the pharmacological reduction of gastric acid secretion. Reducing the acidity of gastric juice ameliorates reflux symptoms and allows esophagitis to heal [10—12]. Nonetheless, incomplete symptom resolution to proton pump inhibitor (PPI) therapy is a common problem in the treatment of GERD and affects a significant proportion of patients who use a PPI once daily [13]. The putative mechanisms for poor symptom response to PPIs include poor compliance, improper timing of PPI consumption, reduced PPI bioavailability, non-acid reflux, visceral hypersensitivity, delayed gastric emptying, psychological comorbidity, and concomitant functional bowel disorders [13,14]. Recently, Cheong et al [15] showed that an abnormal Hill's gastroesophageal flap valve (GEFV) was a significant factor predicting poor response of GERD to PPI treatment. However, whether other factors including pretreatment symptom profiles, rapid PPI metabolism, obesity, metabolic syndrome, and *H. pylori* infection status play important roles in poor symptom response in GERD patients is unclear.

The aims of this study were (1) to examine the rate of incomplete symptoms response following 8-week PPI therapy in patients with mild erosive esophagitis (Los Angeles Grade A/B) and (2) to determine the independent factors predicting incomplete symptom response in patients with mild erosive esophagitis.

Methods

Patients

This study was a multicenter trial. From January 2010 to July 2012, patients between the ages of 15 years and 80 years with (1) clinical symptoms of acid regurgitation, heartburn, or feeling of acidity in the stomach and (2) endoscopic examination showing Los Angeles Grade A or B erosive esophagitis [16] were recruited for the study. Criteria for exclusion included (1) coexistence of peptic ulcer or gastrointestinal malignancies, (2) coexistence of serious concomitant illness (for example, decompensated liver cirrhosis and uremia), (3) previous gastric surgery, (4) allergy to esomeprazole (Nexium, Astrazeneca, 21F, No. 207, Dunhua South Road, Section 2, Taipei City), (5) symptom score of a validated questionnaire (Chinese GERDQ) < 12 [17], (6) pregnancy, (7) frequent (> 3 times/wk) use of hypnotics. Written informed consent was obtained from each patient.

Study design

On enrollment, patients were requested to complete a Chinese GERDQ [17]. In the scoring system, the GERD symptoms included acid regurgitation, heartburn, and feeling of acidity in the stomach. The severity and frequency of symptoms were graded on a 5-point Likert scale as follows: none (no symptoms/none in the past year); mild (symptoms can be ignored/$<$ once monthly); moderate (awareness of symptoms but tolerated easily/ $\geq$ once

monthly); severe (symptoms sufficient to interfere with normal activities/ $\geq$ once weekly); and incapacitating (incapacitating symptoms hindering daily activities or requiring a day off work/ $\geq$ once daily). A cut-off score of $\geq$ 12 achieved the highest accuracy for the diagnosis of symptomatic GERD in the previous study [17]. We therefore only recruited patients with scores of Chinese GERDQ $\geq$ 12.

The body mass index (BMI) of each patient was checked on enrollment. Also, blood sampling for genotyping of *CYP2C19* (cytochrome P450 2C19) was carried out. Gastric biopsy over the antrum and body for *H. pylori* examination was performed during the initial endoscopy. The recruited patients were treated with esomeprazole (Nexium, Astrazeneca, 21F, No. 207, Dunhua South Road, Section 2, Taipei City) 40 mg daily for 8 weeks. During the study period, they were asked to record symptoms with diary cards. The patients returned to the clinic for drug refills and handed in symptom diary cards every 4 weeks. The major outcome measurement was incomplete symptom response, which was defined as experiencing reflux symptoms (acid regurgitation, heartburn, or feeling of acidity in the stomach) sufficient to result in troublesome feelings in the patient during the previous 7 days of treatment.

Demographic data of patients

A complete medical history and demographic data were obtained for each patient, including age, sex, medical history, history of smoking, alcohol, coffee and tea consumption, and duration, frequency, and severity of reflux symptoms.

H. pylori examination

Two biopsy specimens were taken from the lesser curvature sites of the antrum and the corpus, respectively. They were fixed in 10% buffered formalin, embedded in paraffin, and sectioned. The sections, 4-μm thick, were stained with a hematoxylin and eosin stain and a modified Giemsa stain to observe the presence of curved rod-shape bacteria on the mucosal surface [18]. Biopsy specimens were assessed by a histopathologist (H.H. Tseng), who was blinded to patient status and the results of other laboratory tests.

Genotyping of CYP2C19

Blood sampling for genotyping of CYP2C19 was carried out prior to endoscopy for the patients who provided informed consent for the genetic study. The *CYP2C19* genotype was determined using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis [19]. Genotypes were classified into three groups: homogeneous extensive metabolizer (homEM, *CYP2C19**1/*CYP2C19**1); heterogeneous extensive metabolizer (hetEM, *CYP2C19**1/*CYP2C19**2 and *CYP2C19**1/*CYP2C19**3); and poor metabolizer (PM, *CYP2C19**2/*CYP2C19**2, *CYP2C19**2/*CYP2C19**3, and *CYP2C19**3/*CYP2C19**3).

Statistical analysis

To determine the independent factors affecting the treatment response and clinical and genetic factors, the Chi-square test or Fisher's exact test was employed to investigate the relationships between the rate of incomplete symptom response and clinical characteristics. The clinical variables included the following: age ($<$ 60 years or $\geq$ 60 years), sex, history of smoking, history of alcohol consumption ($<$ 80 g/d or $\geq$ 80 g/d), ingestion of coffee ($<$ 1 cup/d or $\geq$ 1 cup/d), ingestion of tea ($<$ 1 cup/d or $\geq$ 1 cup/d), coexistence of a systemic disease (yes or no), insomnia (difficulty in falling asleep $>$ 15 minutes after going to bed $\geq$ 1 d/wk), grade of erosive esophagitis, BMI, genotype of *CYP2C19*, and *H. pylori* status. All statistical analyses were performed using the SPSS program (version 10.1; SPSS Inc., Chicago, IL, USA). A p value $<$ 0.05 was considered to be statistically significant. The variables found to be significant by univariate analysis were subsequently assessed by a stepwise logistic regression method to identify independent factors for incomplete symptom response.

Results

Patient characteristics and endoscopic characteristics

In total, 232 patients [mean age $\pm$ standard deviation (SD), 52.7 $\pm$ 11.5 years; male/female, 126/106] participated in this study. Table 1 shows the demographic data of these participants. Among them, the frequencies of heartburn, epigastric acidic discomfort, and acid regurgitation were 62.1%, 74.1%, and 88.8%, respectively. Fifty patients (21.6%) had hiatal hernia, and 37 patients had an abnormal Hill's GEFV [Grade III: 26 (13.8%); Grade IV: 11 (5.8%)]. The frequencies of homEMs, hetEMs, and PMs of *CYP2C19* genotypes in these patients were 35%, 53%, and 12%, respectively. The prevalence of *H. pylori* infection was 24%.

Univariate analysis for incomplete symptom response in patients with mild erosive esophagitis

Following 8-week esomeprazole therapy, 50 (21.6%) of the erosive esophagitis patients had incomplete symptom response. Table 2 shows the associations between incomplete symptom response and patient characteristics (including clinical, genetic, and bacterial factors on enrollment). The incidence of incomplete symptom response was higher in females than in males (27.4% vs. 16.7%). Additionally, alcohol consumption, underlying diseases, regurgitation of food, chest pain, globus (sensation of a lump or foreign body in the throat), and insomnia were significantly associated with incomplete symptom response ($p = 0.006$, $p = 0.023$, $p = 0.010$, $p = 0.013$, $p = 0.009$, and $p < 0.001$, respectively). However, advanced age, *CYP2C19* genotype, smoking, coffee and tea consumption, high BMI, and *H. pylori* infection were not significantly associated with incomplete symptoms response.

Multivariate analysis for incomplete symptom response in patients with mild erosive esophagitis

Table 3 shows the independent factors predicting incomplete symptom response. Multivariate analysis with

Table 1 Demographic data of patients with mild erosive esophagitis.

Characteristics	Patients with mild erosive esophagitis (n = 232)
Clinical factors	
Age (y; mean ± SD)	52.7 ± 11.5
Sex (male/female)	126/106
Smoking	
(−)	196 (84.5)
(+)	36 (15.5)
Alcohol consumption	
(−)	180 (77.6)
(+)	52 (22.4)
Ingestion of coffee	
(−)	122 (52.6)
(+)	110 (47.4)
Ingestion of tea	
(−)	99 (42.7)
(+)	133 (57.3)
Ingestion of spicy food	
(−)	131 (56.5)
(+)	101 (43.2)
Ingestion of sweet food	
(−)	89 (38.4)
(+)	143 (61.6)
Underlying diseases	
(−)	139 (59.9)
(+)	93 (40.1)
BMI	
< 25	123 (53.0)
≥ 25	109 (47.0)
Endoscopic findings	
Erosive esophagitis	
Grade A	170 (73.3)
Grade B	62 (26.7)
Hiatal hernia	
(−)	182 (78.4)
(+)	50 (21.6)
Hill's GEFV	
Grade I/II	152 (80.4)
Grade III/IV	37 (19.6)
H. pylori status	
(−)	176 (75.9)
(+)	56 (24.1)

Data are presented as n (%), unless otherwise indicated.
BMI = body mass index; GEFV = gastroesophageal flap valve; *H. pylori* = *Helicobacter pylori*; SD = standard deviation.

stepwise logistic regression showed that globus [95% confidence interval (CI): 1.185—4.897; p = 0.015] and insomnia (95% CI: 1.289—3.018; p = 0.002) on enrollment were independent risk factors for incomplete symptom response with odds ratio (OR) = 2.4 and OR = 2.0, respectively (Table 3).

Discussion

Currently, limited information is available on predictors of the response to PPI treatment in patients with erosive esophagitis. In this study, we demonstrated that 21.6% of the patients with Los Angeles Grade A/B erosive esophagitis had incomplete symptom resolution to 8-week esomeprazole treatment. The incomplete symptom response rate ranged from 28% to 59% in previous studies (Table 4). The wide range of symptom response rate is probably due to different study populations, types of PPI use, duration of PPI therapy, and definition of poor symptom response. In this study, globus and insomnia on enrollment were independent risk factors predicting incomplete symptom response in these patients. Other patient characteristics including Hill's GEFV, *CYP2C19* genotype, and *H. pylori* status were not significant independent factors related to incomplete symptom response.

Globus is a persistent or intermittent nonpainful sensation of a lump or foreign body in the throat between meals [20]. The etiology of globus is still unclear but appears to be multifactorial including GERD, abnormalities of the upper esophageal sphincter, visceral hypersensitivity and psychiatric disorders, and stress [21]. GERD has been suggested to be a major cause of this symptom [22,23]. Two basic mechanisms have been proposed to explain the association between GERD and the globus sensation: (1) direct irritation and inflammation of the laryngopharynx by retrograde flow of gastric contents; and (2) vasovagal reflex hypertonicity of the upper esophageal sphincter triggered by acidification of the distal esophagus [24—26]. In this study, the frequency of globus in Los Angeles Grade A/B erosive esophagitis patients was 49.6% (115/232). Multivariate analysis revealed that globus before PPI therapy was an independent factor predicting incomplete symptom response in patients with mild esophagitis. Currently, the reasons for poor symptom response in erosive esophagitis patients with globus remain unclear. Nonetheless, erosive esophagitis patients with globus might have more acidic refluxate reaching upper esophagus and larynx than those without globus. Double-dose PPI has been recommended for the treatment of extraesophageal symptoms of GERD [27,28]. Therefore, the single-dose PPI used in this study might be insufficient to control symptoms in some of our patients with globus. It is also important to note that globus is common in conjunction with reflux symptoms, and a strong relationship between GERD and globus has not been well established [29]. Due to its multi-pathogenesis nature, globus does not appear to respond well to antireflux therapy.

In this study, insomnia is another independent factor predicting incomplete symptom response. The symptom affected 13.8% (32/232) of the erosive esophagitis patients in the current study. Previous studies showed that gastroesophageal reflux is a major cause of disrupted sleep due to awakenings from heartburn, dyspepsia, acid brash, coughing, or choking [30]. However, it is noteworthy that insomnia is not a symptom; instead, this is a disorder. It can be induced by excessive nocturnal reflux or nonreflux factors such as stress and psychological disorders. Therefore, the association between insomnia and incomplete symptom response in this study is possibly due to excessive nocturnal reflux or psychological factors in patients with mild erosive esophagitis [31,32]. The exact mechanism underlying the associations between insomnia and incomplete symptom response merits further studies.

Table 2 Univariate analysis for incomplete symptom response in patients with mild erosive esophagitis.

Characteristics	No. of patients	Incomplete symptoms response	*p*
Clinical factors			
Sex			
Female	106	29 (27.4)	0.049*
Male	126	21 (16.7)	
Age			
< 60 y	165	33 (20.0)	0.367
≥ 60 y	67	17 (25.4)	
Smoking			
(−)	196	44 (22.4)	0.438
(+)	36	6 (16.7)	
Alcohol consumption			
(−)	180	46 (25.6)	0.006*
(+)	52	4 (7.7)	
Ingestion of coffee			
(−)	122	28 (23.0)	0.585
(+)	110	22 (20.0)	
Ingestion of tea			
(−)	99	27 (27.3)	0.067
(+)	133	23 (17.3)	
Ingestion of spicy food			
(−)	131	32 (24.4)	0.225
(+)	101	18 (17.8)	
Ingestion of sweet food			
(−)	89	20 (22.5)	0.788
(+)	143	30 (21.0)	
Underlying diseases			
(−)	139	23 (16.5)	0.023*
(+)	93	27 (29.0)	
BMI			
< 25	123	31 (25.2)	0.151
≥ 25	109	19 (17.4)	
Symptom profiles			
Acid regurgitation			
(−)	26	3 (11.5)	0.188
(+)	206	47 (22.8)	
Heartburn			
(−)	88	16 (18.2)	0.329
(+)	144	34 (23.6)	
Epigastric acidity			
(−)	60	11 (18.3)	0.481
(+)	172	39 (22.7)	
Epigastric fullness			
(−)	93	22 (22.7)	0.524
(+)	139	28 (20.1)	
Regurgitation of food			
(−)	143	23 (16.1)	0.010*
(+)	89	27 (30.3)	
Nausea			
(−)	166	33 (19.9)	0.326
(+)	66	17 (25.8)	
Vomiting			
(−)	206	46 (22.3)	0.417
(+)	26	4 (15.4)	
Belching			
(−)	111	25 (22.5)	0.731
(+)	121	25 (20.7)	
Chest pain			
(−)	142	23 (16.2)	0.013*
(+)	90	27 (30.0)	
Dysphagia			
(−)	194	38 (19.6)	0.100
(+)	38	12 (31.6)	
Globus			
(−)	117	17 (14.5)	0.009*
(+)	115	33 (28.7)	
Sore throat			
(−)	194	42 (21.6)	0.935
(+)	38	8 (21.1)	
Hoarseness			
(−)	169	36 (21.3)	0.879
(+)	63	14 (22.2)	
Cough			
(−)	178	36 (20.2)	0.372
(+)	54	14 (25.9)	
Insomnia			
(−)	200	35 (17.5)	< 0.001*
(+)	32	15 (46.9)	
Laboratory tests			
CYP2C19 genotype			
HomEM	62	10 (16.1)	0.199
HetEM	95	19 (20.0)	
PM	21	4 (19.0)	
Endoscopic findings			
Hiatal hernia			
(−)	188	45 (23.9)	0.068
(+)	44	5 (11.4)	
Hill's GEFV			
Grade I/II	152	29 (19.1)	0.727
Grade III/IV	37	8 (21.6)	
Erosive esophagitis			
LA Grade A	170	40 (23.5)	0.225
LA Grade B	62	10 (16.1)	
H. pylori infection			
(−)	176	40 (22.7)	0.677
(+)	56	11 (19.6)	

Data are presented as *n* (%), unless otherwise indicated.
*$p < 0.05$.
BMI = body mass index; *CYP2C19* = cytochrome P450 2C19; GEFV = gastroesophageal flap valve; hetEM = heterogeneous extensive metabolizer; homEM = homogeneous extensive metabolizer; *H. pylori* = *Helicobacter pylori*; LA = Los Angeles; PM = poor metabolizer.

PPIs, such as omeprazole, esomeprazole, lansoprazole, and pantoprazole, are metabolized by CYP2C19 in the liver. There are genetic differences in the activity of this enzyme [33]. These *CYP2C19* genotypic differences in pharmacokinetics and pharmacodynamics of PPIs influence the healing of erosive esophagitis [34] and eradication rates of *H. pylori* infection by PPI-based regimens [35]. In this study, the incomplete response rate in homEMs, hetEMs, and PMs was

Table 3 Multivariate analysis for incomplete symptom response in patients with mild erosive esophagitis.

Clinical factor	Coefficient	Standard error	OR (95% CI)	*p*
Globus	0.879	0.362	2.409 (1.185—4.897)	0.015
Insomnia	0.679	0.217	1.973 (1.289—3.018)	0.002

CI = confidence interval; OR = odds ratio.

response in PPI therapy for patients with mild erosive esophagitis.

In conclusion, 21.6% of the patients with Los Angeles Grade A/B erosive esophagitis fail to complete symptom resolution following 8-week PPI therapy. Globus and insomnia are two independent factors for incomplete symptom response in patients with mild erosive esophagitis.

Table 4 The frequencies of poor symptom response in patients with gastroesophageal reflux disease.

Authors	Patients (no. of cases)	PPI use	Duration of PPI use (wk)	Definition of poor response	Frequency of poor symptom response (%)
Cheong et al [15]	EE (n = 119)	Pantoprazole, (40 mg daily)	8	$\leq$ 50% reduction in symptom scores	28
Zerbib et al [36]	NERD + EE (n = 100)	Various kinds of PPI (standard or double-dose PPI daily)	$\geq$ 4	$\geq$ 2 d of mild symptoms per wk under PPI treatment	57
Carlsson et al [37]	NERD + EE (n = 538)	Omeprazole (20 mg daily)	4	Completely symptom free during Wk 4	59
Bate et al [38]	NERD + EE (n = 112)	Omeprazole (20 mg daily)	4	More than mild symptoms in the previous 7 d	34
Current study	EE (n = 232)	Esomeprazole (40 mg daily)	8	Reflux symptoms sufficient to lead to troublesome feelings during the previous 7 d	22

EE = erosive esophagitis; NERD = nonerosive reflux disease; PPI = proton pump inhibitor.

16%, 20%, and 19%, respectively. There were no significant differences in response rates among the three groups of patients.

Although Cheong et al [15] showed that abnormal GEFV was a significantly independent factor predicting poor response to pantoprazole treatment in GERD patients, the current study did not find differences in treatment response between patients with different grades of GEFV. The reason for the conflicting results is unclear and merits further investigation.

This study has several limitations. First, only the patients with mild erosive esophagitis were recruited for this study. Whether or not the identified risk factors for incomplete symptom response to PPI therapy can be applied to patients with nonerosive reflux disease (NERD) or severe erosive esophagitis remains unanswered. Second, the study was carried out in a single country. The data will need to be confirmed in regions with different ethnic populations. Third, the study did not use a questionnaire to assess the psychological status of the enrolled patients. Whether psychological factors (such as depression and anxiety) could be the main causes for the refractory symptoms as well as insomnia and globus is still unclear. Fourth, insomnia in this study was defined only by subjective evaluation with the questionnaire; therefore, it may not reflect an actual diagnosis of insomnia. However, this is the first work that simultaneously evaluates multiple clinical, endoscopic, and genetic parameters by multivariate analysis to identify the risk factors of incomplete treatment

Conflicts of interest

All authors declare no conflicts of interest.

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